Department of Health & Human Services   **Public Health Service**

Memorandum   **Food and Drug Administration**
                                            Center for Biologics Evaluation and Research
                                            Office of Therapeutics Research and Review

DATE: October 28, 1998

FROM: Lisa G. Rider, MD, Medical Officer, Division of Monoclonal Antibodies and
             Adjunct Clinical Reviewer, Division of Clinical Trial Design and Analysis

RE: Biological License Application Review for Enbrel (recombinant human
             tumor necrosis factor receptor Fc fusion protein, rhu TNFR:Fc), BLA no.
             98-0286 (Initial submission May 6, 1998; Interim Safety Update, July 21, 1998;
             IND 5088)

FINAL ACTION DATE: November 6, 1998

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TO: File

SUBJECT: Clinical review of juvenile rheumatoid arthritis (pediatric use)

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I. BACKGROUND.

Juvenile rheumatoid arthritis (JRA) is the most common rheumatic disease in children, with a prevalence of 57 = 113 per 100,000 children under the age of 16 in the United States (Singsen 1990). JRA is a group of illnesses characterized by chronic, idiopathic synovitis, with onset prior to 16 years of age. These disorders have been divided into clinically distinct subsets based on the extent of joint involvement and extra-articular manifestations, including the subsets pauci-articular, poly-articular and systemic-onset JRA. Recent long-term follow-up studies have suggested that JRA is not benign, with approximately 30% of patients developing severe functional disability, 31-55% with unremitting synovitis, and ≤ 1% dying from their illness (Wallace 1991). Approximately one-third of JRA patients achieve control of their disease with nonsteroidal anti-inflammatory drugs (NSAIDS) and physical and occupational therapy. A large randomized controlled trial in children with polyarticular course JRA whose disease was resistant to NSAIDs and other agents demonstrated efficacy of methotrexate (MTX) compared to placebo, with an acceptable safety profile (Gianni.i 1992). However, even when MTX is used in adequate doses, some patients fail to respond or respond only partially (Lovell 1997).

In the Draft Guidance for Industry for the Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA), the Agency has outlined a policy for drug development for JRA which encourages sponsors licensing products for adult RA to simultaneously obtain dosing and safety data in polyarticular course JRA for inclusion in the dosing and pediatric use sections of the label. For agents in a new pharmacologic class which are not yet approved for adult RA, sponsors desiring a labeled indication for use in JRA are advised to perform full efficacy studies in JRA, which include all subsets of JRA. If the agent is efficacious in JRA and provided that the data do not suggest the agent is ineffective in any one JRA subset, the label would reflect the JRA subsets included in the efficacy study.

In accordance with the Draft Guidance Document for RA and based on discussions with the Agency, Immunex has submitted one open-label treatment study of polyarticular-course JRA patients for review under the BLA, which has included pediatric pK data, open-label responses to Enbrel in JRA, and safety data for inclusion in the dosing and pediatric use sections of the label. The application is noteable as the first JRA study to be submitted simultaneously with a licensure application for adult RA;

II. PHARMACOKINETIC STUDY

The dose of Enbrel used in the JRA study of 0.4 mg/kg or a maximum dose of 25 mg administered subcutaneous twice weekly was based on a phase II study in adult RA. In this study, 16.0 mg/m2 demonstrated maximal efficacy, which was converted to a 25 mg fixed dose.

Population pharmacokinetic modeling using ————— software was used to assess the pharmacokinetic profile of Enbrel in patients 4-17 years of age with polyarticular course JRA. A total of 202 sample time points from 47 JRA patients were used for the analysis. Serum samples were collected before administration of the study drug on days 1 and 15, and at the end of months 1,2, and 3; and 30 days after discontinuation of study drug (or at the end of Month 4 for patients continuing into part 2 of the study). These samples were to be collected at random times with respect to time of administration of most recent dose of the drug.

The sponsor modeled post-hoc clearance vs. age. The sponsor states that children with JRA had reduced clearance compared to adults. The impact of age was characterized by an Emax model that predicts a clearance of 0.0353 L/h in a 5 year-old JRA patient, while a 50 year-old patient with adult RA is predicted to have a clearance of 0.0681 L/h. Clearance at young ages (e.g., 4 years) appear much reduced compared to adult RA, with a linear increase in clearance by age until age 12-15 years, when the slope of clearance approximates that of adult RA. When clearance was adjusted for body surface area, the average clearance was 45.9 mg/hr/m2 in children with JRA, which was comparable to a similarly-adjusted adult clearance of 52 ml/hr/m2. No change in clearance over age was observed when adjusting by body surface area. Several deficiencies in the modeled clearance data include an absence of information regarding timing of the pK sampling relative to dose administration and time into the dosing regimen. Post-hoc data samples are not available for this submission.

The average serum concentration (Cmax) after repeated dosing was 2.1 mcg/ml with a range of 0.7 to 4.3 mcg/ml. Concentration time curves showed very similar concentration time profiles for a 10 year-old child with JRA compared with a 40 year old adult RA patient for a period up to 40 days. Younger children (ages 4-5), or longer time points are not included in this analysis.

Additional pK parameters for JRA are not provided in the BLA. Specific line listings for JRA pK data are not included in the BLA submission. Furthermore, population pK is thought not to be an appropriate model, based on the finding that the adult RA pK parameters do not appear to achieve a steady state. Finally, JRA pK data were not analyzed separately, but merged with adult RA pK data.

III. CLINICAL TRIAL DESIGN AND CONDUCT

A. Study Design. An open-label multi center study (protocol 16.0016) involving nine sites was conducted, administering Enbrel at 0.4 mg/kg, 25-mg maximum twice weekly subcutaneously to JRA patients 4-17 years of age with a polyarticular course. Responses were assessed at baseline and days 15, 30, 60 and 90, using the JRA Definition of Improvement (DOI) [Giannini, 1997]. The sponsor modified the JRA DOI from that validated by Giannini et al, such that loss of motion (LOM) required the presence of pain and/or tenderness. Blinded, trained joint assessors, who were not involved in the patients' care, performed the joint assessments. Patients were permitted to remain on a stable dose of a single NSAID and/or corticosteroid at a dose of ≤ 0.2 mg/kg or 10 mg maximum. Safety assessments performed at each evaluation included symptoms of toxicity by history and an adverse event diary, vital signs and physical exams, laboratory studies, including hematology profile, chemistry profile, and urinalysis. Autoantibodies (ANA, ENA, anti-dsDNA, and anti-cardiolipin antibodies [ACLA]), and anti-TNFR:Fc were obtained periodically. Patients who responded in part 1 of the study (JRA DOI at 90 days) continued into part 2, which involved a randomized withdrawal of Enbrel to measure efficacy by examining flare rate and time to flare. Part 1 of the study is submitted with the BLA.

Inclusion criteria:
• Between 4 and 17 years of age.
• Diagnosis of JRA by American College of Rheumatology criteria; disease onset pauciarticular, polyarticular or systemic.
• Polyarticular disease course.
• Disease must have been refractory to MTX or patient must have been intolerant of MTX (physician defined).
• At screening, ≥ 5 swollen joints and ≥ 3 joints with LOM accompanied by pain and/or tenderness.
• No treatment with DMARDs, intravenous immunoglobulin, cytotoxic agents or intra-articular steroids within 28 days before receipt of study drug. No treatment with MTX at least 14 days before dosing with study drug.
• Stable hematocrit of ≥ 24 %.
• Prepubescent and not expected to reach puberty for at least 8 months, or practicing adequate contraception if postpubertal and sexually active; not pregnant.

Exclusion Criteria:
• Functional class IV by ACR criteria.
• Platelet count < 100,000 cells/cmm; total white cell count < 4000 cells/cmm; neutrophils < 1000 cells/cmm; hepatic transaminase levels > 2 times upper limit of normal (ULN); bilirubin > 2 times ULN; and creatinine clearance < 90 mL/min/1.73 smm BSA or a GFR of < 90 mL/min/1.73 smm BSA.
• Positive tests for HIV, HBsAg, or hepatitis C antibody, or anti-dsDNA.
• Previous receipt of anti-TNF, anti-CD4, or DAB-IL-2.

• Participation in an investigational drug or biologic study within past 3 months.
• History of current psychiatric illness; history of alcohol or drug abuse.
• Any concurrent medical condition which would, in the Investigator's opinion, compromise the patient's ability to tolerate the study drug or comply with the protocol.

Response Assessments. In order to be randomized into part 2, the efficacy portion of the study, patients had to demonstrate disease response after 90 days of open-label treatment with TNFR:Fc. To be considered a responder, patients had to demonstrate a response as defined by the JRA DOI, which includes $\geq$ 30% improvement in at least three of the six following criteria, with $\leq$ 30% worsening in not more than one of the six assessments: physician's global assessment, patient/parent global assessment, number of active joints (swelling not due to deformity or joints with LOM plus pain and/or tenderness), number of joints with LOM (modified by sponsor to include LOM plus pain and/or tenderness), functional assessment (Childhood Health Assessment Questionnaire [CHAQ] (Singh 1994), and ESR (Giannini, 1997). Additional response assessments included articular severity score, pain score, duration of morning stiffness and C-reactive protein (CRP). Joint assessors were trained and blinded to the patient's clinical care.

B. Patient Population.
In protocol 16.0016, 54 polyarticular-course JRA patients were submitted to the BLA for analysis of treatment responses. Sixty-nine JRA patients were incorporated into the updated integrated safety summary, which was submitted to the Agency on July 21, 1998, although line listings for the 15 additional patients were not available for safety review and they were not included in the treatment response review. Fifty-one (94%) of the 54 patients completed Part I of the study. Three patients prematurely discontinued the study: two because of lack of efficacy and one due to patient/parent refusal (also lack of efficacy).

Of the 54 patients submitted in the original BLA filing, 11% had pauciarticular-onset, 59% had polyarticular-onset, and 21% had systemic-onset JRA. Mean patient age was 10.3 $\pm$ 3.8 years (range 4 - 17 years) and subjects had JRA an average of 5.6 $\pm$ 3.0 years (range 0.7 - 12.3 years). Sixty-one percent were girls. In terms of racial distribution, 74% were Caucasian, 7% African American, 15% Hispanic, 2% Asian (East Indian), and 2% Native American. Twenty-one percent were rheumatoid factor positive. Mean baseline active joint count was 29 $\pm$ 14 joints (range 10 - 63) and mean baseline LOM was 14 $\pm$ 13 joints (range 0 - 47). All patients had received MTX in the past; 85% had disease refractory to MTX and 15% were intolerant of MTX. Patients received on average 2.4 other anti-rheumatic agents (DMARDs, cytotoxics, or intravenous immunoglobulin) prior to study entry; 24% had also received experimental therapy. At study entry, 94% were receiving NSAIDs and 33% were receiving corticosteroids. In summary, the patient population had JRA that was more severe than an average university clinic population of JRA patients.

C. Study conduct: Protocol deviations and compliance.
Thirteen patients (24%) did not meet the inclusion criteria of $\geq$ 3 joints with LOM and pain or tenderness at screening. Their responses for the JRA DOI would have remained unchanged, even

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if LOM was not included in their JRA DOI responses, except for one nonresponder, who would have been a responder if LOM was not included. Regarding ancillary medications while on study, 5 patients (9.2%) changed NSAID medication, increased dose of existing NSAID, or began a new NSAID during the study protocol. Three patients (2 responders, 1 nonresponder) received prednisone at doses > 10 mg daily. One responder received an intra articular glucocorticoid injection for a Baker's cyst. One patient who developed urticaria after the first dose of TNFR:Fc, withdrew at that time and was not included in the efficacy data, but was included in the updated safety summary. Two patients who had anti-dsDNA autoantibodies at screening were assigned a patient number, but received no doses of medication and were not included in the study. Four patients (7%) missed one dose of TNFR:Fc; one patient (2%) missed two doses of medication.

IV. RESPONSE TO THERAPY ANALYSIS.

A. Primary endpoint.

Results of the open-label JRA trial pertaining to the primary endpoint, the JRA DOI, are summarized in the table below:

Table 1: 90 Day Responses for JRA, Using JRA Definition of Improvement
Overall JRA Responses and Responses by Disease Onset Subset.

	90 Day JRA DOI Responses
Overall	41/54 (76%)
By Onset Subset:	
Pauciarticular Onset	3/ 6 (50%)
Polyarticular Onset	26/32 (81%)
Systemic Onset	12/16 (75%)

Three patients who dropped out of the protocol were included in CBER's analysis using last observation carried forward. Ninety-day responses using the JRA DOI were 76% overall, and 50-81% in the various onset subset types (pauciarticular, polyarticular, systemic onset, p> 0.26 for responses by subset).

CBER also analyzed whether JRA DOI responses at 90 days varied by demographic factors or baseline disease activity. CBER found no differences in JRA 90 day response rates, using the JRA

DOI, by age (including by logistic regression), rheumatoid factor status, study site, gender, glucocorticoid use, disease duration (including by logistic regression), baseline active joint count (including by logistic regression), baseline CHAQ scores (including by logistic regression), and baseline weight, height, or body surface area (logistic regression) [see Appendix 1, Tables 1 - 8 and Figures 1 - 2 , for specific results].

B. Secondary endpoints.

Median 90 day responses for the individual components of the JRA DOI, as well as for articular severity score, pain scores (measured on 10 cm visual analog scale), morning stiffness, and CRP, were also analyzed by CBER (Table 2).

Table 2: Percent change in median 90 day responses for components of the JRA DOI and other secondary endpoints.

Percent Change in Secondary Endpoints:	Median Percent Change in 90 Day Responses [25%, 75%]
Active Joint Count	-56% [-30,-76]
LOM	-73% [0, -100]
Physician Global	-67% [-29, -100]
Patient/Parent Global	-50% [0, -100]
- CHAQ	-33% [-11,-83]
ESR	-52% [- 9, -73]
Articular Severity Score	-48% [-17,- 48]
Pain (VAS)	-64% [-17,-93]
Morning Stiffness	-71% [0,-97]
CRP	-64% [-16,-93]

C. Summary.

Enbrel appears to have comparable responses at 90 days for polyarticular course JRA as in adult RA, although the data are open-label and conclusions regarding efficacy in JRA cannot be made until part 2 of the study has been completed. The responses in JRA do not appear to differ by disease onset subset (pauciarticular, polyarticular and systemic onset JRA), or by any other clinical or demographic parameter examined, although the power to conduct such subset analyses is limited. Younger patients do not have enhanced clinical responses compared to older children

in this open label study. Responses in objective laboratory measures (ESR, CRP) appeared comparable to other parameters of disease activity.

V. SAFETY ANALYSIS.
Analysis of safety is based on the 54 JRA patients who completed part 1 of the study (90 days) at the time of original BLA filing, for whom detailed line listings were available for CBER's review. Comparison of JRA safety to adult RA safety was done with the data provided in the Updated Integrated Safety Summary and includes all 69 JRA patients. Adverse event (AE) data was obtained by review of patient diary and histories, physical examinations, laboratories (chemistries, hematology, urinalysis, autoantibodies). The NCI Common Toxicity Criteria was modified for pediatric use to grade the severity of AEs. A separate infectious disease questionnaire was used to capture infectious disease severity. Adverse events were classified using a modified Coding Symbols for a Thesaurus of Adverse Reaction Terms dictionary (COSTART 1990).

For comparisons of JRA vs. adult RA frequencies of AEs, CBER's analysis was based on the updated Integrated Safety Summary submitted to CBER on July 21, 1998. This safety update included data from 69 JRA patients who had completed part 1 of the study, although detailed line listings were not provided for the 15 additional patients included in that submission. In comparing JRA vs. adult RA regarding frequencies of AEs, that analysis was performed primarily to examine whether any AEs were obviously seen in greater frequency in JRA compared to adult RA, to further examine the impact of decreased clearance of the product in younger children compared to adults. This analysis is problematic due to a few confounding factors: JRA patients were exposed to Enbrel for shorter durations (90 days) compared to adult RA (primarily 6 months). Also, 59 adult RA patients received Enbrel in combination with MTX, whereas no JRA patients received this combination. The analysis of JRA vs. adult RA had to be performed in this manner due to the manner in which summary data was provided in the updated integrated safety summary.

A. Adverse events.
Constitutional AEs in part 1 of the JRA, from CBER's review of AE line listings, are summarized in Table 3.

Table 3. Constitutional Adverse Events (non-infectious) by Decreasing Frequency for 54 JRA patients completing 90 Days Treatment with TNFR:Fc.

Event	Number of Patients (%)	Number of Events	Grade	Relationship to Product
None	14 (26%)			
Headache	10 (19%)	16	1	unrel-prob
Abdominal pain	10 (19%)	10	1-2	unrel-poss
Vomiting	7 (13%)	8	1	unrel-prob
Rash	7 (13%)	7	1	unrel-poss
Accidental injury (fx, sprain, lac, bite)	6 (11%)	6	1	unrel
Nausea	5 (9%)	9	1-2	unrel-poss
Fatigue	4 (7.4%)	5	1	unrel-poss
Cough	3 (5.5%)	3	1	unrel-poss
Diarrhea	3 (5.5%)	3	1	unrel
Dizziness	3 (5.5%)	3	1	unrel-poss
Edema	3 (5.5%)	3	1-2	unrel-prob
Fever	3 (5.5%)	3	1-2	unrel-poss
Injection site bruise	3 (5.5%)	3	1	unrel
Mouth sore/ulcer	3 (5.5%)	3	1	unrel
Pain-back,chest	3 (5.5%)	3	1-2	poss
Drowsiness/somnolence	1 (1.8%)	2	1	poss
Compression fx	1 (1.8%)	1	3	unrel
Anorexia	1 (1.8%)	1	1	unrel
Dry mouth/throat	1 (1.8%)	1	1	poss
Enuresis	1 (1.8%)	1	1	unrel
Jaundice	1 (1.8%)	1	1	unrel
Perianal fissure	1 (1.8%)	1	1	unrel
Pseudoporphyria	1 (1.8%)	1	1	unrel
Acne exacerbation	1 (1.8%)	1	1	unrel

Noninfectious AEs were generally mild-moderate in severity. No differences in the frequencies of specific AEs were observed by age (breaking age down 4-8 years vs. 9-17 years, or 4-12 years vs. 13-17 years) or by gender. No differences in the number of AEs were observed by disease onset subset, except headache was seen predominantly in polyarticular onset JRA (n=9/32 patients [28%], vs. n=1/16 [6.3%] for systemic onset JRA vs. 0/6 for pauciarticular JRA, p=0.096).

Gastroinestinal intolerance was observed more frequently in JRA patients than adult RA patients treated with Enbrel. Abdominal pain occurred in 12/69 JRA patients (17%) vs. 46/617 patients with adult RA (7%) [p=0.01]; vomiting was seen in 10/69 JRA patients (14.5%) vs. 21/617 patients with adult RA (3%), [p < 0.001]. Gastrointestinal symptoms in JRA were not apparently related to the use of NSAIDs: 14/16 [88%] of patients with abdominal pain or vomiting were taking NSAIDs vs. 38/38 [100%] of patients without these symptoms were on NSAIDs. Headache was observed more frequently in JRA than adult RA (16/69 [23%] of JRA vs. 102/617 [17%] of adult RA), but this was not statistically different. The frequency of 25 other AEs, occurring in ≥ 3% of patients, did not differ between JRA and adult RA .

Laboratory abnormalities. Five of 54 JRA patients (9.2%) developed lymphopenia during the first 90 days of treatment with Enbrel; all were grade 1 or 2. Three of these patients had a persistent decline in lymphocyte count. JRA patients developed lymphopenia less frequently than adult RA patients (24/68 [35%] in JRA vs. 414/612 [68%] adult RA, p<0.001). Four JRA patients (7.4%) experienced 6 transient episodes of neutropenia; all were grade 1 or 2. Four patients (7.4%) had grade 1 decreases in total white blood count; 3 of the episodes were transient. Nine patients (17%) developed grade 1 increases in alanine aminotransferase during the first three months on study, seven of which were isolated events, and six patients (11%) developed a grade 1 increase in aspartate aminotransferase, four of which were transient. One patient developed a grade 3 elevation in bilirubin, which began on day 1 of treatment and persisted throughout the 90 days; this patient has Gilbert syndrome. One patient developed a grade 1 transient increase in serum creatinine, and no patients had abnormalties on their urinalyses. Overall, laboratory events were mild, transient, and not necessarily related to the product.

Serious adverse events and deaths. No deaths were observed in the JRA study. Several serious AEs developed during the study, some of which were unrelated to the product. In the updated integrated safety summary, one patient was reported with aseptic meningitis 9 days after varicella infection, as well as a vertebral artery thrombosis and compression of the inferior medulla related to cervical subluxation (C1-C2) [Grade 3]. This patient had a lymphocytosis of the cerebral spinal fluid, with negative cultures for bacteria and viruses, as well as negative PCR for varicella. The patient's anti-cardiolipin IgG was negative at baseline and day 92, but not available at the time of the vertebral artery thrombosis. The aseptic meningitis was thought by the investigator to be possibly related to the product, and the vertebral artery thrombosis was considered to be unrelated and due to cervical subluxation with resultant compression of the vertebral artery. A second case of headache, nausea and vomiting following varicella infection is reported in the updated integrated safety summary, and is not noted to be serious; additional information is unavailable at this time. Both patients resolved their varicella infections without sequelae. The product's

relationship to these probable cases of aseptic meningitis following varicella infection is unclear, as aseptic meningitis may be observed as an immune-mediated phenomenon following natural varicella infection.

One patient was hospitalized for intravenous fluids related to gastroenteritis (Grade 3). One patient was hospitalized for a beharioral problem during the study which was unrelated to product. One patient developed a vertebral compression fracture (Grade 3), but had been treated previously with repeated pulses of corticosteroids, and this was thought to be unrelated to product. One patient had a Grade 3 elevation in bilirubin, which began on day 1 of treatment with Enbrel and persisted through the 90 day study; this was thought by the investigator to be due to Gilbert's syndrome.

B. Infectious complications.

Line listings were available for CBER's review from the first 54 JRA patients who completed part 1 of the study. Eighteen of 54 JRA patients (33%) experienced one infection, 9 patients (17%) had 2 infectious episodes, and 5 patients (9%) had 3-5 infectious episodes during the 90 day open-label study. All infections were grade 1 or 2. Patients were generally on study medication from September until January, although a few patients began the protocol in July and completed by October. The infectious complications are reported in Table 4.

Table 4. Infectious events for 54 JRA patients completing 90 days of treatment with TNFR:Fc.

Event	Number of Patients (%)	Number of Events
Upper respiratory infection	17 (32%)	18
Pharyngitis	9 (17%)	11
Gastroenteritis	5 (9%)	5
Otitis media	5 (9%)	6
Conjunctivitis	2 (3.7%)	2
Sinusitis	2 (3.7%)	2
Flu syndrome	1 (1.8%)	1
Impetigo	1 (1.8%)	1
Parotitis	1 (1.8%)	1
Paronychia	1 (1.8%)	1
Skin-viral lip lesion	1 (1.8%)	1
Vaginitis	1 (1.8%)	1

There was no association of infectious complications with age: 4/21 patients (19%) 4 - 8 years of age vs. 7/32 patients (22%) 9 - 17 years of age developed an infection on treatment. Of the patients with more than one infectious episode, 4 were ages 4-8 and 7 were ages 9-13 years. There was no association of infections with corticosteroid use during the study: 14/20 patients receiving steroids (70%) vs. 18/34 children (53%) not on steroids developed an infection. There was also no association of infections with disease onset subset: 2/6 (33%) pauciarticular vs. 23/32 (72%) polyarticular vs. 8/16 (50%) systemic-onset JRA patients developed an infection while receiving Enbrel.

Some infections were observed more frequently in JRA patients than adult RA: pharyngitis (10/69 [14.5%] in JRA vs. 28/565 [5%] in adult RA), gastroenteritis (8/69 [11.6%] in JRA vs. 19/565 [3.4%] in adult RA), and otitis media (6/69 [8.7%] in JRA vs. 14/565 [2.5%] in adult RA). Upper respiratory infections were less frequent in JRA compared to adult RA: 26/69 (38%) in JRA vs. 395/565 (70%) adult RA. Of note, an analysis by the sponsor combining JRA and adult RA patients revealed that the low dose group (< 10 mg) had a higher infection rate (3.8 episodes per year) compared to the mid dose (10-25 mg) [1.7 infectious episodes per year] and the high dose (> 25 mg) [1.7 episodes per year], p =0.05. Rates of infections specifically for JRA patients were not provided in the submission.

Two cases of probable aseptic meningitis associated with varicella infection have previously been discussed under serious adverse events (p. 10).

C. Injection site reactions and allergic complications.

Of 54 JRA patients who completed 90 days of treatment with Enbrel for whom detailed line listings could be reviewed by CBER, 18 (33%) experienced 1 - 4 injection site reactions and 6 patients (11%) had > 4 injection site reactions, which consisted of erythema, swelling, pruritus, and/or pain. On average, 1.7 injection site reactions occurred per patient in the study protocol. Seventy-one of 94 injection site events (76%) were grade 2; the remainder were grade 1. Injection site reactions were not associated with age (12/32 [38%] in 4-12 years vs. 10/22 [31%] in 13-17 years) or disease onset subset (3/6 [50%] pauciarticular vs. 11/32 [34%] polyarticular vs. 6/16 [38%] systemic onset JRA). The frequency and number of injection site reactions was comparable in JRA and adult RA patients: 21/69 (30%) of JRA vs. 172/617 (28%) of adult RA patients had 1-5 injection site reactions, 6/69 (9%) of JRA vs. 87/617 (14%) of adult RA had > 5 injection site reactions.

Two patients in the JRA study developed urticaria while receiving Enbrel. One patient developed urticaria after the first dose of product and did not receive any additional medication. A second patient developed urticaria on day 9 (grade 1) and completed the study without additional episodes. One patient developed eczema (grade 1) on day 36. No other allergic or hypersensitivity complications were observed.

D. Autoantibodies and immune-mediated adverse events.

Three of 54 (5.6%) of JRA patients completing 90 days of treatment with TNFR:Fc developed a positive anti-nuclear antibody (ANA) during the study. Two patients (3.7%) increased their titer of ANA on treatment. Two patients who were ANA positive at baseline developed a decrease in titer on study, and one patient with a positive ANA at baseline had no change in titer over 90 days.

None of the patients developed a positive extrable nuclear antigens (ENA) or Rheumatoid factor during the 90 day study. One patient was positive for anti-Sm autoantibody at baseline, and one patient was borderline positive for ENA at baseline, but specific autoantibodies (Ro, La, Sm and U1-RNP) were negative. Eleven patients (21%) had a positive rheumatoid factor at baseline.

Four patients of 69 (5.8%) developed positive anti-dsDNA autoantibodies, detected by radioimmunoassay, during the first three months on study. These patients titers were low positive (3.8 - 4.5 IU/ml, upper limit of normal = 3.5 IU/ml). None of these patients had symptoms of systemic lupus erythematosus. Specific testing of these children by the _____ Crithidia luciliae assay will be requested.

Regarding anti-cardiolipin antibodies, testing was problematic because three different lots of assay reagents were used to test patients' sera. Eighteen of 54 JRA patients (33%) developed anti-cardiolipin IgG autoantibodies within the first three months on study. None of these patients developed thrombotic events. Two patients positive for anti-cardiolipin IgG at baseline remained positive at day 90, and three patients positive at baseline lost reactivity to cardiolipin at day 90. The sponsor plans to submit an update of the anti-cardiolipin test results upon completion of part 2 of the study, which will use a single lot of assay reagents. Preliminary review of this updated data in a FAXed copy revealed that four of 69 JRA patients (5.8%) developed IgG and one patient (1.4%) developed IgM anti-cardiolipin antibodies after receiving Enbrel for four months.

The patient with vertebral artery thrombosis had tested negative for anti-cardiolipin IgG on two occasions up to day 90, but results of testing at the time of the event or subsequently are not available. There was no association of anti-cardiolipin antibodies with age or disease onset subset.

No JRA patient developed a specific autoimmune disease during the first three months of the study.

E. Malignancy.

No JRA patients developed a malignancy after receiving TNFR: Fc.

F. Summary.

From a database of 54 JRA patients with detailed AE data and a comparison of 69 JRA patients to 617 adult RA patients, the frequency of AEs in JRA appears to be comparable to adult RA, except for an increase in gastrointestinal intolerance in JRA patients, manifest as abdominal pain and vomiting. Adverse events are predominantly mild to moderate in intensity. Increased frequencies of certain infections in JRA patients are expected based on the natural history of these infections in pediatric vs. adult populations. Adverse event rate data are not available for JRA patients, and because JRA patients were not treated, on average, for as long a duration as adult RA patients, the comparison of the frequency of adverse events in JRA to adult RA is problematic. The role of TNFR:Fc in mediating aseptic meningitis following varicella infection is unclear. Forty-four percent of JRA patients developed injection site reactions and 3.7% developed urticaria. The development of anti-dsDNA autoantibodies occurred in 5.8% of JRA patients within the first 90 days of therapy; 33% of JRA patients developed anti-cardiolipin antibodies in the same period. No specific autoimmune events have been observed related to these autoantibodies, but additional testing is needed of these patients to determine the specificity and frequency of these autoantibodies.

Addendum:

Concluding from the Arthritis Advisory Committee meeting on September 16, 1998, the committee concluded that responses to immunization, particularly with live viral vaccines, had not been studied and that patients should not receive live vaccines while receiving Enbrel therapy. It was recommended that, when possible, pediatric patients be brought up to date with immunization schedules prior to receiving Enbrel, and that patients should temporarily discontinue treatment with Enbrel when there is a necessity for them to receive such immunizations.

The panel also recommended that Enbrel be temporarily discontinued when a patient without a prior history of varicella infection has a significant exposure to varicella and that they also receive Varicella Zoster Immune Globulin.

VI. TELECONFERENCES WITH SPONSOR.

A teleconference was held with the sponsor on July 9, 1998 to discuss the pediatric pK data submitted to the BLA, as well as to clarify a few issues in the JRA clinical submission. Dr. David Green from CBER discussed the apparent reduced clearance of product in younger children compared to adult RA patients. The sponsor agreed to provide more detailed explanation of the pediatric conclusions, post hoc analysis plots of age vs. Clearance; if using post-hoc clearance, they would estimate steady state values of children vs. Adults; and they would lay out a rationale as to why children could be considered part of the adult population and analyzed together.

Regarding the JRA clinical section, the sponsor clarified the normal range for ENA testing, to be 20-25 =borderline positive; > 25 = positive. This is true also for specific testing of SSA, SSB, Sm,

U1RNP, Scl and Jol. For dsDNA antibodies, the normal range in children and adults is 0-3.59 U. For anticardiolipin antibodies, it was clarified that the Reeds kit materials are identical to Sigma reagents for testing the presence of these antibodies. However, the Reed assay kits varied a lot, depending on the lot number used. The sponsor plans to retest anticardiolipin antibodies at the end of the trial using kits from the same lot number. To date, no thrombotic events have been recorded. The sponsor also provided an update of serious adverse events which would be included in the updated Integrated Safety Summary.

A second teleconference was held with the sponsor on August 27, 1998, in which request for information was made for the Pediatric Labeling Supplement, which is planned for filing later in the year.

VII. QUESTIONS TO THE ARTHRITIS ADVISORY COMMITTEE.

The current license application contains information from the first phase of the pediatric study, the open-label, uncontrolled, phase; data from the randomized portion were not available for inclusion in the BLA. If approved for use in adult patients with rheumatoid arthritis, labeling could include the information from the uncontrolled phase (e.g., numbers of patients studied, ages, doses, adverse events, etc.) As well as the statement "safety and efficacy below the age of 16 have not been established."

VIII. ISSUES FOR SPONSOR.

THIS PAGE WAS DETERMINED TO BE NOT RESPONSIVE TO YOUR REQUEST

pages 16 and 17

APPENDIX 1: SUBSET ANALYSES FOR 90 DAY RESPONSES, USING JRA DEFINITION OF IMPROVEMENT (DOI).

Table 1: 90 Day Responses for JRA, using JRA DOI. Responses by Age

Age	90 Day JRA DOI Response
4 - 8 years	16/21 (76%)
9 - 12 years	6/11 (54%)
13 - 17 years	19/22 (86%)
p value (Chi squared)	0.13

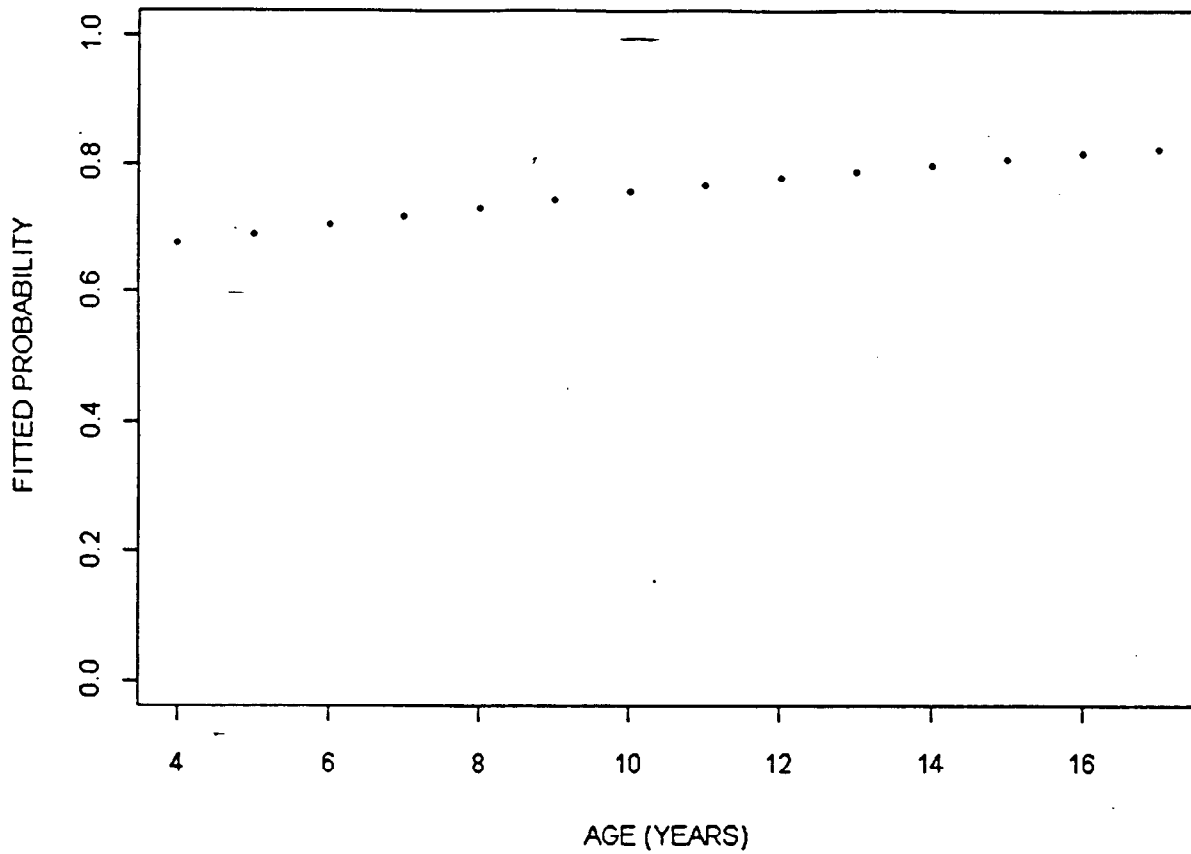Fitted Probability of JRA DOI Response by Age
Study 16.0016

Figure 1: Logistic Regression

Estimate for age ± SEM: 0.06 ± 0.08, p=0.44

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Table 2: 90 Day Responses for JRA, using JRA DOI. Responses by Rheumatoid Factor Status.

Rheumatoid Factor Status:	90 Day JRA DOI Response
Positive	9/11 (82%)
Negative	31/42 (78%)
p value (Chi squared)	0.73

Table 3: 90 Day Responses for JRA, Using JRA DOI. Resposes by Study Site.

Study Site Number:	90 Day JRA DOI Response
31	7/ 8 (88%)
174	2/ 6 (33%)
182	3/ 6 (50%)
242	4/ 5 (80%)
502	3/ 4 (75%)
503	10/10 (100%)
504	3/ 4 (75%)
506	2/ 2 (100%)
514	7/ 9 (78%)
p value (Chi squared)	0.12

Table 4: 90 Day Responses for JRA, using JRA DOI. Responses by Gender.

Gender:	90 Day JRA DOI Response
Female	27/33 (82%)
Male	14/21 (67%)
p value (Chi squared)	0.20

Table 5: 90 Day Responses for JRA, using JRA DOI. Responses by Glucocorticoid Use.

Glucocorticoid Use:	90 Day JRA DOI Response
Yes	16/20 (80%)
No	25/34 (74%)
p value (Chi squared)	0.59

Table 6: 90 Day Responses for JRA, using JRA DOI. Responses by Disease Duration.

Disease Duration:	90 Day JRA DOI Responses
0 - 4 years	16/22 (73%)
4 - 8 years	16/19 (84%)
> 8 years	9/13 (69%)
p value (Chi squared)	0.56

Logistic Regression: Estimate $\pm$ SEM for disease duration: 0.07 ± 0.11, $p = 0.54$.

Figure 2: Logistic Regression for Baseline Active Joint Count vs. 90 Day JRA DOI Responses.

Estimate $\pm$ SEM for baseline active joint count: -0.03 $\pm$ 0.02, p = 0.21

Fitted Probability of JRA DOI Response
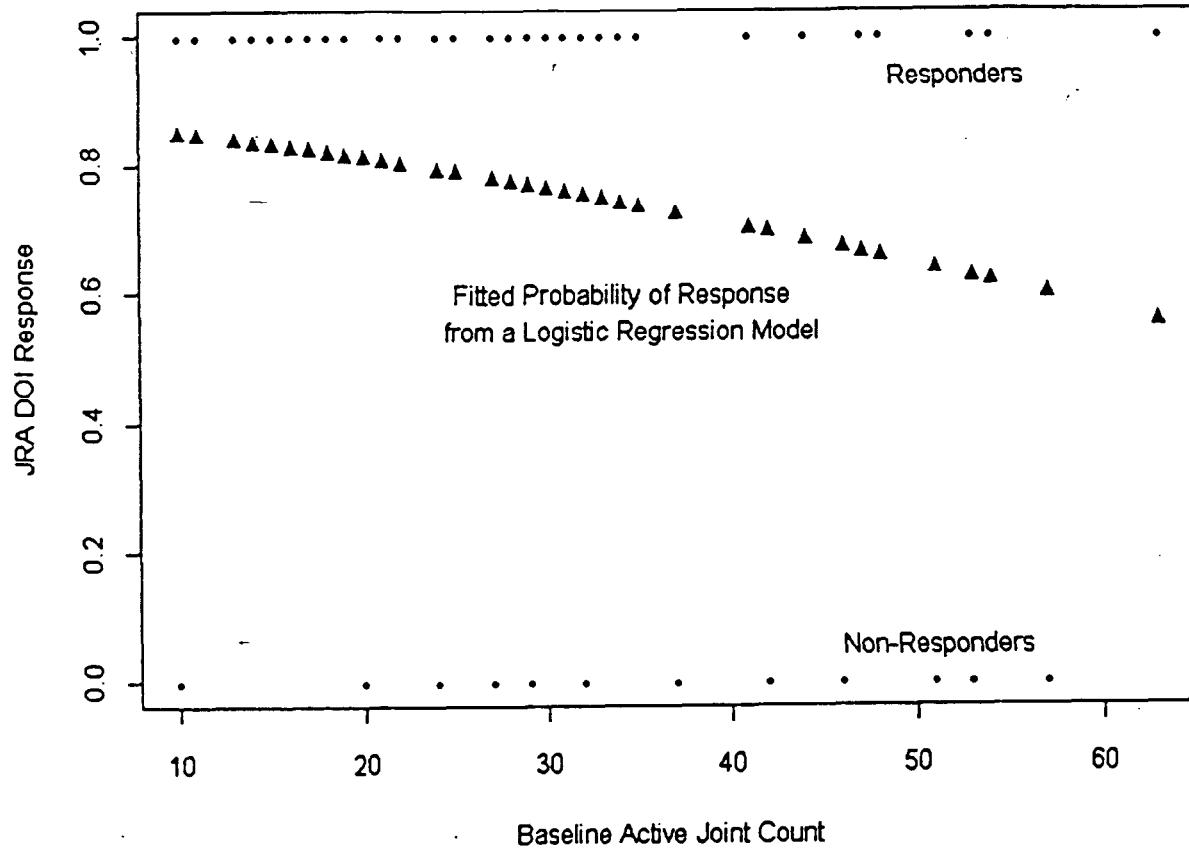## by Baseline Active Joint Count, Study 16.0016

Table 7: 90 Day JRA DOI Responses using JRA DOI. Responses by Baseline CHAQ.

Baseline CHAQ Scores:	90 Day JRA DOI Response
0 - 1	12/13 (92%)
1 - 2	14/22 (64%)
2 - 3	15/19 (79%)
p value (Chi squared)	0.15

Logistic Regression: Estimate $\pm$ SEM for baseline CHAQ scores: -0.05 $\pm$ 0.07, p = 0.51.

Table 8: 90 Days JRA DOI Responses using JRA DOI. Responses by weight, height and body surface area, using Logistic Regression.

	Estimate $\pm$ SEM	p value
Weight	0.04 $\pm$ 0.02	0.08
Height	0.01 $\pm$ 0.01	0.33
Body Surface Area	1.8 $\pm$ 1.1	0.09

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